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GREEN TEA POLYPHEONOLS: A LITERATURE REVIEW

Pranjal Ray [1] | Dr. Bhupen Kalita [2]

[1] M. Pharm, Pharmaceutics, Girijananda Chowdhury Institute of Pharmaceutical Science, PO: Azara, Dist: Kamrup, Guwahati-781017, Assam, India.

[2] Asstt. Professor, Pharmaceutics, Girijananda Chowdhury Institute of Pharmaceutical Science, PO: Azara, Dist: Kamrup, Guwahati-781017, Assam, India.

ABSTRACT

Green tea is manufactured from the leaves of the plant Camellia Sinesis and belonging to the family Theaceae and is used most popularly as beverage all over the world. The major components of Green tea which are responsible for the potential pharmacokinetic properties, Antioxidant and other Health benefits are Polyphenols. The major polyphenols in Green tea are Flavonoids. The Flavonoids present in Green tea is Catechins these are mainly four type, Epicatechin (EC), Epigallocatechin (EGC), Epicatechin gallate (ECG) and Epigallocatechin gallate (EGCG). The most significant active component is Epigallocatechin gallate (EGCG). Human studies found that long term consumption of Green tea catechins could be beneficial against, Cardiovascular activity, as Antioxidant, Antibacterial activity, Anticancer properties, Dental caries and Diabetic properties etc. Further research that conforms to international standards should be performed to monitor the pharmacological and clinical effects of green tea and to elucidate its mechanisms of action.

KEYWORDS: Polyphenols, Catechins, Compositions, Pharmacokinetics, Health benefits.

INTRODUCTION

Polyphenols

Polyphenols, a large class of chemicals which are found in plants, have attracted much attention in the last decades due to their properties and the hope that they will show beneficial health effects, when taken as a dietary input or as complement.[1] Phenolic compounds constitute one of the most extensive group of chemicals in the plant kingdom. It is estimated that more than 8000 compounds have been isolated and described.[2]

Polyphenols are polyhydroxylated phytochemicals, which have common structures. They can be subdivided in three main subclasses, the flavonoids, phenolic acids, and the stilbenoids. By far most isolated compounds belong to the subclass of the flavonoids. Flavonoids are characterized as containing two or more aromatic rings, each bearing one or more phenolic hydroxyl groups, and connected by a carbon bridge.[3,4] One aromatic ring (A ring) is connected to the second aromatic ring (B ring) by a carbon bridge which consists of three carbon atoms. When the three carbon chain is connected to a hydroxyl group from A, the formed structure become cyclic (C ring), as a 6-membered ring. Most flavonoids bear this type of phenylbenzopyrane structure: they have further been subdivided into subclasses, based on the position of the B ring relative to the C ring, as well as the functional groups (ketones, hydroxyls) and presence of a double bond or not in the C ring. These subclasses are termed flavones, isoflavones and isoflavanes, flavanones, flavanols, anthocyanidins, chalcones and dihydrochalcones. The flavanols themselves are subdivided into monomers (catechins) and polymers (proanthocyanidins, theaflavins and thearubigins). [4]

Phenolic acids are usually divided in two main groups. They are derived from benzoic acids, containing seven carbon atoms, or from cinnamic acids, comprising nine carbon atoms.[5] All these compounds are hydroxylated. The main representative isolated compounds are gallic acid, chlorogenic acid, caffeic acid, ferulic acid, p-coumaric acid, and gentisic acid.

The smaller subclass of stilbenoids comprises polyhydroxylated stilbenes, the main representative being resveratrol. All these polyphenols are found in plants, esterified with glucose and other carbohydrates (glycosides) or as free aglycones. This contributes to their complexity and the huge number of individual substances which have been isolated and identified. Dietary polyphenols have been isolated from fruits (berries, apples, citrus, cherries); vegetables (onion, celery, beer hops, soy beans)[6] herbs, roots, spices (gingko, turmeric); green and black tea; red wine. It is known that consumption of flavonoid-rich foods, especially fruit and vegetables, translates into benefits on human health: epidemiological studies have found associations between lower incidence of heart disease, cancer, gastrointestinal and neurological diseases, liver diseases, atherosclerosis, obesity and allergies.[2,5,7,8,9]

Polyphenols are potent antioxidants; they are able to scavenge free radicals. It was first thought that the health benefits associated with the consumption of dietary polyphenols were due to antioxidant mechanisms. There is conflicting evidence however on how great the contribution of the total antioxidant capacity in human plasma results in increased antioxidant protection of lipids and proteins. Other limiting factors are a low solubility of the aglycones (often less than 20mg/ml water), low absorption, and a rapid metabolism. Many of the positive effects were demonstrated *in vitro* and research has been done on animal populations, therefore the benefits on humans remain uncertain. Poor bioavailability of polyphenols, usually in a range of 2-20%, makes it even more difficult to draw clear conclusions and relevant data from small clinical trials.[1] It is also believed, but has not been conclusively proven, that the metabolites are less or barely biologically active.

Nevertheless, there is mounting evidence and an accumulating number of studies which report the neuroprotective, cardioprotective and chemopreventive actions of dietary polyphenols. Despite the major focus on the antioxidant properties, there is an emerging belief that flavonoids and other polyphenols, and their metabolites, do not act as antioxidants, but may exert modulatory actions in cells through actions at protein kinase and lipid kinase signalling pathways.[10] Polyphenols from green tea exert their effect on multiple signalling pathways and regulate cell cycle proteins (Cyclin D1 as an example), protein kinases (e.g. IKK, Akt, MAPK), growth factors (e.g. EGF, HER-2), transcription factors (e.g. NF-κB, PPAR, p53), proapoptotic proteins (caspases, PARP, Bax and Bak) and anti-apoptotic proteins (e.g. Bcl-2, Bcl-Xl, TRAF1).[9]

A good deal of the recent research has been conducted on citrus flavonoids and on polyphenols found in green tea. Antibacterial, antitoxin, antiviral and antifungal activities of those compounds have been demonstrated.[11] As concluding remarks we would like to cite Halliwell and his word of caution: "Flavonoids and other polyphenolic compounds have powerful antioxidant effect *in vitro* in many test systems, but can act as pro-oxidants in some others. Phenolic compounds may help to protect the gastrointestinal tract against damage by reactive species present in foods or generated within the stomach and intestines.[12]

Green tea polyphenols

Tea is one of the most popular beverages consumed worldwide. Tea, from the plant Camellia sinensis, is consumed in different parts of the world as green, black, or Oolong tea. Among all of these, however, the most significant effects on human health have been observed with the consumption of green tea [13]. The first green tea was exported from India to Japan during the 17th century. It is estimated that about 2.5 million tons of tea leaves are produced each year throughout the world, with 20% produced as green tea, which is mainly consumed in Asia, some parts of North Africa, the United States, and Europe.[14] The association between tea consumption, especially green tea, and human health has long been appreciated.[15] Green tea and black tea are processed differently during manufacturing. To produce green tea, freshly harvested leaves are immediately steamed to prevent fermentation, yielding a dry, stable product. This steaming process destroys the enzymes responsible for breaking down the color pigments in the leaves and allows the tea to maintain its green color during the subsequent rolling and drying processes. These processes preserve natural polyphenols with respect to the health-promoting properties. As green tea is fermented to Oolong and then to black tea, polyphenol compounds (catechins) in green tea are dimerized to form a variety of theaflavins, such that these teas may have different biological activities.

The major catechins in green tea are (-)-epicatechin (EC), its hydroxyl derivative(-) epigallocatechin (EGC), and their respective gallic acid esters, (-)-epicatechin-3-gallate (ECg) and (-)-epigallocatechin-3-gallate (EGCg). Among green tea catechins, EGCg is abundant in green tea leaves, and has beenshown to exhibit strong health-promoting activity[16], according to structure activity relationship assessment on EGCG, two close parallel aromatic rings and a third aromatic ring vertical to the two parallel rings may play a key role in the pharmacophore activity. This activity may be associated with the number of -OH groups in the catechin.[17]

Green tea composition

The chemical composition of green tea is complex: proteins (15-20% dry weight), whose enzymes constitute an important fraction; amino acids (1-4% dry weight) such as theanine or 5-N-ethylglutamine, glutamic acid, tryptophan, glycine, serine, aspartic acid, tyrosine, valine, leucine, threonine, arginine, and lysine; carbohydrates (5-7% dry weight) such as cellulose, pectins, glucose, fructose, and sucrose; minerals and trace elements (5% dry weight) such as calcium, magnesium, chromium, manganese, iron, copper, zinc, molybdenum, selenium, sodium, phosphorus, cobalt, strontium, nickel, potassium, fluorine, and aluminum; and trace amounts of lipids (linoleic and a-linolenic acids), sterols (stigmasterol), vitamins (B, C, E), xanthic bases (caffeine, theophylline), pigments (chlorophyll, carotenoids), and volatile compounds (aldehydes, alcohols, esters, lactones, hydrocarbons). Due to the great importance of the mineral presence in tea, many studies have determined their levels in tea leaves and their infusions. Fresh leaves contain, on average, 3-4% of alkaloids known as methylxanthines, such as caffeine, theobromine, and theophylline.[18] Green tea contains polyphenols, which include flavanols, flavandiols, flavonoids, and phenolic acids; these compounds may account for up to 30% of the dry weight. Most of the green tea polyphenols (GTPs) are flavonols, commonly known as catechins. Products derived from green tea are mainly extracts of green teain liquid or powder form that vary in the proportion of polyphenols (45-90%) and caffeine content (0.4-10%).

The major flavonoids of green tea are various catechins, which are found in greater amounts in green tea than in black or Oolong tea. There are four kinds of catechins mainly find in green tea: epicatechin, epigallocatechin, epicatechin-3-gallate, and EGCG.[19] The preparation methods influence the catechins both quantitatively and qualitatively; the amount of catechins also varies in the original tea leaves due to differences in variety, origin, and growing conditions.[20] The preparation of fresh green tea cannot totally extract catechins from the leaves; therefore, the concentration found differs from the absolute values determined through the complete extraction of leaves.[21] Moreover, catechins are relatively unstable and could be quantitatively and qualitatively modified during the time frame of an experiment [22]. Thus, comparison of ingested doses in animal studies is not possible because the catechin quantification before administration is often not known.

Mechanism of action

The retardation of the growth and development of neoplasm by inhibition of tumour initiation and promotion, induction of apoptosis, and inhibition of cell replication rates is due to the anticarcinogenic properties of green tea polyphenols.[23] The polyphenols antioxidant potential of green tea is directly related to the combination of aromatic rings and hydroxyl groups that make up their structure and is a result of binding and neutralization of free radicals by the hydroxyl groups. In addition, the activity of hepatic detoxification enzymes is stimulated by green tea polyphenols, thereby promoting detoxification of xenobiotic compounds and are also capable of chelating metal ions, such as iron, that can generate radical oxygen species. The production of arachidonic acid metabolites such as pro-infl ammatory prostaglandins and leukotrienes is inhibited by green tea polyphenols, which results in a decreased inflammatory response. EGCG has the ability to block inflammatory responses to ultraviolet A and B radiation, as well as, significantly inhibiting neutrophil migration that occurs during the infl ammatory processand this has been demonstrated by human and animal studies. There exists a synergistic interaction between green teas caffeine content and catechin polyphenols that can result in prolonged stimulation of thermogenesis. Studies have also shown green tea extracts are capable of reducing fat digestion by inhibiting the activity of certain digestive enzymes.[24,25] Although the exact mechanism is unknown, green tea catechins have been shown to significantly raise levels of Lactobacilli and Bifi dobacteria while at the same time decreasing the levels of numerous potential pathogens. Green tea demonstrates antibacterial properties against a variety of gram-positive and gram-negative species.[26] Other than acting as antioxidants, polyphenols have additional mechanisms in which they reduce oxidation level: (1) It binds metal ions such as iron and copper and prevents their participation in oxidation reactions, forming hydroxyl radical. (2) Prevents redox sensitive transcription factors activation that amongst others things serve as mediators of inflammatory reactions. (3) Suppresses oxidation stimulants such as induced nitric oxide synthase (iNOS), cyclooxygenase 2 (COX-2), lipoxygenase 2 (LOX-2) and xanthine oxidase.(4) Induction of antioxidant enzymes like glutathione S-transferase and super oxide dismutase.[27]

Pharmacokinetics of tea polyphenols

A number of papers reported the pharmacokinetics of tea polyphenols. The half-lives of tea polyphenols are 2-4hrs and their absorption and elimination are rapid in humans. The peak times (t max) are 1 and 3 h after oral administration and the peak plasma concentrations are low μM range. There are some controversial issues in pharmacokinetics of tea polyphenols, such as the competitive absorption effect and variable oral bioavailability. The saturation absorption and competition absorption would occur in the gastrointestinal tract at high doses of tea catechin extracts. Further tea polyphenols undergo extensive biotransformation *in vivo*, which may interfere with the observation of the pharmacokinetic properties of tea polyphenols.[28,29,30]

Pharmacomkinetics of (-)-epicatechin (EC):

Some literature reported the plasma pharmacokinetics of EC in rats, rabbit, dogs, and humans. When a mixture of catechins was administrated, because of competing for binding to plasma protein or inhibiting the glucuronidation and sulfation, the pharmacokinetic behaviour of each catechin could be influenced by the other catechin. Pure EC at lower dose was administrated to rabbits by intravenous, intraperitoneal, and oral route. EC showed dose-independent pharmacokinetics after intravenous administration. The area under the concentration-time curve (AUC) was proportional to the dose over the range 5-25 mg/kg. After intraperitoneal administration of 25 mg/kg, a high percentage of EC escaped from first-pass hepatic elimination. After oral administration of 50 mg/kg, there was a great variation in the pharmacokinetics, and the mean oral bioavailability of EC was 4%.[30] EC was absorbed very quickly with a Cmax of 202.6 ± 21.1 nM around 1–2 h after ingestion, and clearance from plasma was also rapid and back to baseline 6–8 h after ingestion with a monophasic response. EC was present predominantly in plasma as conjugates, and the conjugated forms of EC were two-thirds as sulfate and one-third as glucuronide.[31] also determined the levels of EC in human plasma after administraton of green tea, and the concentration was 11.0 ng/mL, being about 1.8% of the administered dose in the 2 h plasma collection. The human volunteers were given different amounts decaffeinated green tea extract (DGT) and the blood and urine concentrations of tea catechins were detected. After consumption of 1.5 g DGT, the average peak plasma concentration (C max) of EC was 0.65 μM. The C max increased with dosage, and C max values did not increase, when the doses were more than 4.5 g. The half-lives of EC were 3.2-5.7h after oral administration of 1.5-4. 5 g of DGT. In addition, pharmacokinetics of EC in rat brain and blood were also studied by microdialysis sampling coupled to high-performance liquid chromatography with chemiluminescence detection. The t1/2 values of EC were 13.67 ± 4.33 min for blood and 41.67 ± 9.14 min for brain. The maximum brain concentrations of EC were observed after about 20 min of administration. EC have relatively short t1/2 in blood and long t1/2 in brain, indicating that EC suffer more intense biotransformation in blood than in brain. The brain distribution ratio (AUCbrain/AUCblood) of EC was 0.1065 ± 0.0531.[32]

Pharmacomkinetics of (−)-epigallocatechin Gallate

Pharmacokinetics experiments showed that EGCG is absorbed rapidly in the gut following oral administration, and membrane permeability of EGCG was low [33] examined the safety, tolerability, and pharmacoketic properties of EGCG in human. Peak concentrations were reached between 1.3 and 2.2 h. When oral doses of EGCG were more than 1000 mg, the maximal plasma EGCG concentrations were greater than 1 μM. Single-dose of EGCG and polyphenon E capsule (containing 200 mg EGCG) were administrated to human. The results showed that if the EGCG doses were same, the pharmacokinetis of EGCG were similar in both formulations The Cmax of EGCG were 0.16, 0.24, 0.37, 0. 96 μM after 200, 400, 600, and 800 mg dose of EGCG, respectively. The average Cmax of EGCG was 0.16, 0.27, 0.36, 0.82 μM after giving Polyphenon E containing 200, 400, 600, and 800 mg EGCG, respectively. EGCG was present in human plasms mostly as un- changed form, which was proved by deconjugating enzymes (β -glucuronidase/sulfatase) experiment [34]. While EGC and EC were present in human plasmas as phase II metabolites. The pharmacokinetics and oral bioavailability studies of green tea catechins were performed in laboratory animals. The oral bioavailability of EGCG in rats was 1.6% when 10 mg/kg EGCG was given by intravenous and 75 mg /kg was administrated by oral route. The oral bioavailabilities of EGCG, EGC, and EC were 0.1%, 13.7%, and 31.2%, respectively, where DGT was also administered to rats via intravenous (25 mg /kg) and oral (200 mg /kg) routes. The bioavailabilities of EGCG were different after pure EGCG and DGT administration, which may come from the effect of other components in DGT on the oral absorption of EGCG and form conjugated metabolites during the pre-systemic first-pass metabolism. The oral bioavailability of unchanged EGCG in mice was about 15.8% and higher than bioavailability in rats. Recent clinical studies have examined tea catechin absorption in the small intestine in individuals with an ileostomy. When 200 mg of Polyphenon E was administrated to patients, the average recovery was 27% for the nongallated catechins, EC and EGC, and was 59% for the gallated catechins, EGCG and ECG, in the ileal fluid.[35] The results were similar after green tea consumption. Therefore, the nongallated catechins are absorbed from the small intestine more efficiently than their gallated analogs.[36] Recently, the pharmacokinetics of crystal EGCG was reported. EGCG cocrystals exhibit far lower aqueous solubilities, increased variability and the Cmax, unchanged Tmax and improved bioavailability.[37]

Pharmacomkinetics of (−)-epigallocatechin and (−)-epicatechin Gallate:

The pharmacokinetics parameters of tea catechins, such as AUC and Cmax, increased with the increasing dose of Polyphenon E. The plasma levels of unchanged EGCG and ECG were higher than that of unchanged EGC and EC.

Gallated catechins, EGCG and ECG, were present in plasma mostly as the unchanged form, where as non-gallated catechins, EGC and EC, were mostly present as the glucuronide and sulfate conjugates. Additionally, Food can also affect the bioavailability of tea catechins. There was a 3- to 5- fold increase in plasma levels of EGCG and ECG when Polyphenon E was taken on an empty stomach after an overnight fast than when taken with food, and the plasma levels of total (unchanged plus glucuronide and sulfate conjugates) EGC did not significantly change, but resulted in lower plasma levels of total EC. Poluphenon E capsules (containing 37 mg EGC) were administrated to human; the levels of EGC were low or undetectable. EGC levels increased substantially after the plasma samples were treated with deconjugating enzymes, so the main metabolites of EGC in plasma were the glucuronide and sulfate conjugates. Green tea and decaffeinated green tea were administrated to rats. Secondary peaks were observed in the pharmacokinetic profiles of each catechin at around 90 min, suggesting the presence of enterohepatic recirculation.[37] Each catechin reached the maximum plasma concentration at 0.6–0.8 h. The variation of time at secondary peak among catechins may be ascribed to the pharmacokinetic differences between gallated catechins and nongallated catechins. The terminal elimination rate of ECG and EGC were 0.009/min and 0.010/min, respectively. The clearance rate of EGC was higher than that of ECG. The bioavailability of catechins with a galloyl moiety was extremely low, whereas EGC had greater bioavailabily than ECG. The opposite result in terminal half-life between intravenous and intragastric administration of green tea was attributed to the difference in the dose administered and the degree of pharmacokinetic interaction among catechins.[38]

Health benefit of green tea polyphenols:

The health benefits of tea have long been recognized in China and Japan. Scientific reports in the last two decades have validated many beneficial claims for tea. Understanding the mechanisms of the biological effects has interested scientists worldwide. The majority of beneficial effects have been attributed to the polyphenolic constituents.[40]

Phenolic compounds are widely distributed in food of plant origin and are regarded as effective antioxidants. Several studies suggest that these components may be of importance in reducing the incidence of degenerative diseases such as cancer and arteriosclerosis.[39] The most relevant compounds in dietary regimens are cinnamic acid derivatives and flavonoids. As natural polyphenols remain unchanged in green tea, it can be said that green tea is more beneficial than black tea, where fermentation during manufacture leads to the oxidation of primary polyphenols. The strong antioxidant potential of tea polyphenols is thought to mediate most of the beneficial effects of tea. Health benefits in relation to cancer, arthritis, cardiovascular diseases, diabetes, obesity and dental caries have been focused on scientific investigations in the recent past.[39]

Cardiovascular Activity

Several flavonoids and related phenolics have been reported to inhibit either enzymatic or non-enzymatic lipid peroxidation, an oxidative process implicated in several pathological conditions including atherosclerosis.[39] In particular, it has been suggested that tea polyphenols lower the oxidation of low-density lipoproteins (LDL) cholesterol, with a consequent decreased risk of heart diseases.[40] It has been observed that green tea polyphenols significantly reduce the levels of serum LDL, very low-density lipoproteins (VLDL) and triglycerides.[41] At the same time, they increase the levels of high-density lipoproteins (HDL). A low ratio of triglycerides to HDL is an excellent marker for cardiovascular health. In a cross-cultural correlation study of sixteen cohorts known as "The Seven Countries Study", the average flavanol intake was inversely correlated with mortality rates due to coronary heart disease after 25 years of follow-up.[42] This observation has been strengthened by the finding that in hypercholesterolemic rats, green tea polyphenols lowered blood cholesterol levels and reduced blood pressure in spontaneously hypertensive animals.[43]

The quantities of antioxidants in the diet are inversely related to the risk of death from heart disease and of non-fatal heart attacks. Green tea inhibits vascular smooth muscle proliferation, which is another factor contributing to the formation of arteriosclerotic plaque.[44] Tea polyphenols also interfere with the absorption of dietary fat and cholesterol. Green tea polyphenols have been found to play an important role in controlling essential hypertension by inhibiting angiotensin-I converting enzyme (ACE), which converts angiotensin-I to vasoconstrictive angiotensin-II.2

Antioxidant properties:

Green tea and its supplements generally contain higher amounts of disease fighting anti- oxidants called polyphenols. A plethora of evidence suggests strong antioxidant potentials of tea flavonoids in suppressing the production of excess free radicals. Major catechins present in green tea i.e. epicatechin (EC), epigallocatechin gallate (EGCG), epigallocatechins (EGC) and epicatechin gallate (ECG) have strong antioxidant potentials. The higher antioxidant activity of green tea makes it more beneficial in protecting the body from oxidative damage due to free radicals. It is appeared that these antioxidants slow or halt the initiation of cancer, heart disease, suppresses immune function and accelerated aging.[45]

EGCG is the most potent one and has also been found to outperform vitamin C and β carotene 10 times in scavenging the allyl peroxyl radical. However, at the same time evidences in a study suggests a reverse correlation between the amount of phenolic compound in green tea and its antioxidant potentials i.e., the quantity of these phenolic compounds is not always correlated with its quality.[46]

Antibacterial activity:

Leaves extracts of green tea indicates the presence of potent antibacterial activity. The green tea polyphenols have been found to be inhibitory against Escherichia coli, Enterococcus faecalis, Salmonella typhi, Staphylococcus aureus and Pseudomonas sp. In a similar study, antibacterial activity of the water and ethanolic extracts of green tea was found against Streptococcus mutans and Lactobacillus acidophilus.[47] Polyphenols in green tea preferentially suppress the growth of pathogenic bacteria in the gut, but not the growth of friendly bacteria. Fairly high concentration of catechins does not harm bifidicts, bacillus (Probiotics), good bacteria which is necessary for the functioning of the intestinal tract. The inclusion of green tea showed positive effects on the increase of lactic acid bacteria and aerobic bacteria counts in ruminants.[48] Acidic, basic and neutral methanol extract fraction of Camellia japonica inhibited the growth of food borne pathogens in microbiological media and food.[49] Green tea is also known to inhibit the reproduction and growth of medically important bacteria, like Salmonella, Clostridium and Bacillus Inhibitory effect of green tea catechins on Helicobacter pylori infection has been reported.[50] Recently antifungal activity of green tea catechins against Candida albicans and Aspergillus fumigates has been explored. These findings suggest that regular consumption of green tea can help us to combat with frequent bacterial infections.

Anticancer properties:

One benefit of consuming green tea is that carcinogenesis in the digestive tract is postulated to be inhibited by ECGC as polyphenols from tea inhibited the growth and disintegration of a human stomach cancer cell line KATO III, and also inhibited tumor necrosis factor-a (TNF-a) release from the cells.[51] The order of polyphenols that followed the inhibition was ECG, EGCG, EGC and the aflavins. Inhibition of TNF -a release from a human stomach cancer cell line (KATO III) took place with the tea polyphenols (ECG, EGCG, EGC) treated with okadiac acid. Gastrointestinal tract cancer is mainly associated with an excess intake of protein and fat.[52] The polyphenols of green tea have been shown to exhibit inhibitory effects on cancer of the gastrointestinal tract and also have shown preventive effects against several other types of cancer. However, the evidence to support the preventive effects of green tea polyphenols on stomach and intestinal cancer is not clear. Studies indicate that green tea has a protective effect on adenomatous polyps and chronic atrophic gastritis formations. The inhibitory effect of green tea polyphenols was studied on the human lung cancer cell line, PC-9.[53] Polyphenols that were examined included EGC, ECG, EGCG, and EC. Comparing their inhibitory effect, ECG and EGC showed the same potency as EGCG but EC showed less inhibitory effect. These studies shows the protective effects of green tea and health benefits associated with it on the cell line studied.

Breast carcinoma is considered to be one of the most common cancers in women.[54] Breast cancer is more prevalent in western countries compared to Japan because of their daily intake of green tea as part of the diet. Consumption of green tea prior to the clinical cancer onset is believed to have decreased the risk of stage I and II breast cancer in women. Drinking green tea is believed to inhibit certain cancers, such as lung, skin, oesophagus, liver, and stomach.[55] Tea catechins are mainly absorbed by the small intestines and are metabolized by enzymatic reactions. Epidemiological studies on the consumption of green tea and risks associated with cancer are still not clear. The reasons for the inconclusive studies might be due to poorly designed studies, differences in lifestyle and metabolic systems of individuals. Oxidative stress plays a major role in several liver diseases. Green tea has an anti-proliferative activity on hepatoma cells, suppresses hepatoma-induced hyperlipidemia (hypercholesterolemia and hypertriglyceridemia), and also prevents hepatotoxicity.[56] Green tea may be a chemo preventive agent for hepato carcinogenesis in the absence of chronic hepatocyte damage. It suppresses D-galactosamine induced liver injury in rats, which could be through inhibition of tumor necrosis factor-induced apoptosis. Daily ingestion of green tea prevented hepatotoxicity (increase in serum glutamic-oxaloacetic transaminase and glutamicpyruvic transaminase; decrease in hepatic glycogen, serum triglyceride, and lactate dehydrogenase) and cell proliferation in the liver of rats on administration of 2-nitropropane.[57]

Most pro-carcinogens require metabolic activation by metabolite enzymes such as phase I and II enzymes in order to convert to electrophiles before they can exert any carcinogenic effects.[58] In limiting the formation of carcinogens, green tea and its catechins promote the elimination of pro-carcinogens such as polycyclic hydrocarbons and heterocyclic amines from the body by inducing phase I cytochromes P450 1A1, 1A2, and 2B1 enzymes and phase II detoxification enzymes, for example, GT.[59] The pro-carcinogen-activating enzyme cytochrome P450 3A4 is also suppressed. 2,3,7,8-Tetrachlorodibenzo-pdioxin (TCDD) is the most toxic compound of dioxin congeners.[60] Exposure of experimental animals to dioxins causes adverse effects such as body weight loss, immunosuppression, endocrine disruption, cancer promotion, teratogenesis, and lethality. Dioxins bind to the cytosolic aryl hydrocarbon receptor (AhR), commonly called the dioxin receptor, resulting in its transformation. Since AhR transformation is the initial step in the expression of dioxin toxicity, inhibition of transformation would protect humans from toxic effects. Theaflavins inhibit the binding of the TCDD to the AhR and also the binding of the transformed AhR to

the specific DNA-binding site as putative mechanisms. Tea extracts can inhibit the cytochrome P450-mediated metabolism of 2-amino-3-methylimidazo, [4,5-f] quinoline (IQ) into its ultimate mutagenic metabolite forms, and interact with both the promutagens and their metabolites in a way that can reduce their mutagenic potential.[61] Benzopyrene (BaP)- and cyclophosphamide (CP)-induced genotoxicity in microbial and mammalian test systems are inhibited in a dose-dependent manner by theaflavins. The polyphenols of black tea are more potent inhibitors of mutagenicity than those of green tea caused by the food mutagen PhIP.[62]

Dental caries:

Various factors like diet, nutrition, the resident oral flora and the host response interact to determine whether infection occurs in a multi factorial condition like dental caries. Any intervention in any of the factors that can reduce its incidence will have a significant impact on public health. Caries can be generally prevented by cleaning teeth. There are reports that tea consumption may decrease dental caries in laboratory animals and humans. The erosion and abrasion of teeth can be protected by mouth rinsing with green tea extract (0.61%).[63] In addition, washing mouth with green tea (1.6 g of pulverised green tea in 40 ml for 3 times a day) for a week was able to significantly reduce the salivary levels of the virulent cryogenic pathogens, Streptococcus mutans and lactobacilli. Such reduction of those pathogens level will decrease the susceptibility to dental caries. The tea extract reduced amylase activity in human saliva. Therefore, tea consumption is likely to be an anti-cryogenic agent which lessens the cryogenic potential of starch containing foods, that leads to less maltose release that causes mineral depletion from tooth enamel.[64,65]

Enough evidences have been collected which shows that the bioactive components of green tea are able to influence the process of caries formation at several differrant stages: by inhibiting proliferation of the streptococcal agent, by interfering with the process of adhesion to tooth enamel or by acting as inhibitors of glucosyl transferase and amylase. Catechins in green tea are inhibitory for S. mutansand S. Sobrinus with 50 and 1000 μg/ml, well within the concentrations found in brewed tea have been reported by many workers.[64] The polyphenol components in the extracts obtained from different teas, affect caries development as they reduce the production of acidic compounds and synthesize streptococci to adherent water-insoluble glucan from sucrose with the cooperative action of glucosyl transferase. The many of the 'flavourcompounds' (e.g. nerolidol) are present in low concentration in green tea. But they might give synergistic effect with the abundant catechins. There is good experimental evidence that catechinscan prevent the attachment of oral streptococcal pathogens to surfaces. Otake et al.in their study, found that the attachment of Streptococcus mutants saliva-coated hydroxyapatite discs is prevented by Sunphenon (a commercial mixture of catechins extracted from green tea leaf) and have demonstrated that EGCG and ECG inhibit streptococcal glucosyltransferase. The effective inhibitors of the enzyme to be catechins fraction of tea and other beverages.[65]

Effect on diabetes:

A study by provided compelling in vitro evidence that EGCG decreases glucose production of H4IIE rat hepatoma cells.[66] The investigators showed that EGCG mimics insulin, increases tyrosine phosphorylation of the insulin receptor and the insulin receptor substrate, and reduces gene expression of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase. Recently, green tea and green tea extracts were demonstrated to modify glucose metabolism beneficially in experimental models of type II diabetes mellitus.[67,68] In addition, EGCG ameliorates cytokine induced b cell damage in vitro and prevents the decrease of islet mass induced by treatment with multiple low doses of streptozotocin in vivo.[69,70]

The intragastric administration of EGCG at a dose of 75 mg/kg resulted in a C max of 128 mg/l total plasma EGCG and a terminal half-life of 83 minutes. Furthermore, in humans an oral intake of EGCG at a dose of 50 mg (0.7 mg/kg) resulted in a C max of 130 mg/l total plasma EGCG and a terminal half-life of 112 minutes.[71] These results indicate that rodents must be orally administered 100- to 600- fold more EGCG (depending on whether they are administered by gavages or by feed admixture) to achieve similar plasma concentrations as those found in humans. Total plasma EGCG concentrations shown to be efficacious in mice and rats can be reached by an Intake of low to moderate doses of EGCG in humans.[71]

Other green tea products:

Knowing the health benefits of tea catechins, new products have been developed with tea as an active ingredient in products such as Ready-To-Drink (RTD) tea beverages, confections, ice creams, cereal bars and pet foods. Some researchers have focused on the incorporation of Green Tea Extract (GTE) into foods, such as bread, cereals, biscuits and dairy products.[72] However, in addition to its bioactive components, green tea is also a rich source of other nutritional substances, such as dietary fibre and protein, which are usually wasted after tea polyphenols extraction.[73] Instead of drinking green tea some people apply green tea bags to their to soothe sunburn and prevent skin cancer due to sun exposure. Green tea bags are also used to decrease puffiness under the eyes as a compress for tired eyes or headache and to stop gums from bleeding after tooth is pulled. Green tea in candy is used for gum disease. Green tea is used in an ointment for genital warts. Drinking green tea with lemon improves the health benefits of the tea, according to researchers at Purdue University; Citrus Juice brings out green tea's anti-oxidants making them more available for your body to absorb.[73] Catechins, which prefer the acid environment of the stomach, become degraded in more alkaline conditions of the small and large intestine, where nutrient absorption takes place. Lemon juice can increase the amount of catechins in body extracts from green tea by up to six times. Further compounds in tea can inhibit iron absorption from foods; drinking green tea with lemon reduces that effect. The combination of honey with green tea has been used since very past as they are very effective in healing wounds.

Adverse effects of green tea:

Although green tea has several beneficial effects on health, the effects of green tea and its constituents may be beneficial up to a certain dose yet higher doses may cause some unknown adverse effects. Moreover, the effects of green tea catechins may not be similar in all individuals. EGCG of green tea extract is cytotoxic, and higher consumption of green tea can exert acute cytotoxicity in liver cells, a major metabolic organ in the body [74]. Another study found that higher intake of green tea might cause oxidative DNA damage of hamster pancreas and liver.[75] The EGCG acts as a pro-oxidant, rather than an antioxidant, in pancreatic b cells in vivo. Therefore, high intake of green tea may be detrimental for diabetic animals to control hyperglycemia. At a high dose (5% of diet for 13 wk), green tea extract induced a thyroid enlargement (goiter) in normal rats.[76] This high-level treatment modified the plasma concentrations of the thyroid hormones. However, drinking even a very high dietary amount of green tea would be unlikely to cause these adverse effects in humans. Harmful effects of tea overconsumption (black or green) are due to three main factors: (1) its caffeine content, (2) the presence of aluminum, and (3) the effects of tea polyphenols on iron bioavailability. Green tea should not be taken by patients suffering from heart conditions or major cardiovascular problems. Pregnant and breastfeeding women should drink no more than one or two cups per day, because caffeine can cause an increase in heart rhythm. It is also important to control the concomitant consumption of green tea and some drugs, due to caffeine's diuretic effects.[77] Some studies revealed the capacity of tea plants to accumulate high levels of aluminum. This aspect is important for patients with renal failure because aluminum can be accumulated by the body, resulting in neurological diseases; it is therefore necessary to control the intake of food with high amounts of this metal.[78] Likewise, green tea catechins may have an affinity for iron, and green tea infusions can cause a significant decrease of the iron bioavailability from the diet.[79]

CONCLUSION:

Green tea is consumed all over the world in various forms. The above studies highlight the extensive Pharmacokinetic properties and health benefits of green tea. The bioactive components in green (EC, ECG, EGC and EGCG) possess Cardiovascular, Antioxidant, Antibacterial, Anticancer, Dental caries and Antidiabetic properties. Based on the above mentioned studies, it can be concluded that due to the purported health benefits of green tea, its consumption and applications have increased to large extent. This review presents various studies supporting green tea's role in maintaining oral health as well as the general health. But further research on this field is still needed to define the actual magnitude of health benefits, so that the mechanisms of action can be elucidated.

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